Magnetic Resonance Imaging Follow-up of Temporomandibular Joint Inflammation, Deformation and Mandibular Growth in Juvenile Idiopathic Arthritis Patients on Systemic Treatment

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Abstract: OBJECTIVE To investigate the course of temporomandibular joint (TMJ) inflammation, osseous deformation and mandibular ramus growth in children with juvenile idiopathic arthritis (JIA) during systemic therapy. METHODS Longitudinal study of 38 consecutive JIA patients (29 female, median age 9.0 years, interquartile range 6.2 to 10.7 years) on systemic therapy with TMJ involvement, with two TMJ magnetic resonance imaging (MRI) examinations 2 years apart and no TMJ corticosteroid injection. Clinical and MRI findings were compared between initial and follow-up examinations and between TMJs with and without active inflammation at baseline. RESULTS Over a median period of 3.6 years (range, 2.0-8.7 years), MRI grade of TMJ inflammation improved (p=0.009) and overall osseous deformity tended to become less severe (p=0.114). In TMJs with arthritis at baseline (46 TMJs), both the grades of inflammation (p<0.001) and deformity (p=0.011) improved. In TMJs with no arthritis at baseline (30 TMJs), the frequency and grade of condylar deformation remained stable. Mandibular ramus growth rates were not significantly different between TMJs with and without arthritis at baseline (1.3 mm/year versus 1.5 mm/year, p=0.273), and were not correlated with the degree of inflammation at baseline or followup. The frequency of facial asymmetry tended to be lower at follow-up than at initial examination (24% versus 45%, p=0.056). CONCLUSION Our results suggest that systemic treatment of TMJ arthritis in children with JIA decreases the degree of inflammation seen on MRI, preserves osseous TMJ morphology and maintains normal mandibular ramus growth.

DOI: https://doi.org/10.3899/jrheum.190168

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DOI: 10.3899/jrheum.190168
http://www.jrheum.org/content/early/2019/09/11/jrheum.190168

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Key Indexing Terms:

Temporomandibular joint, Juvenile idiopathic arthritis, Therapy, Magnetic resonance imaging, Outcome research

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This research received no specific grant from any funding agency in the public, commercial or non-for-profit sectors. The authors declare that they have no conflict of interest.

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Short running head:

TMJ MRI in JIA on systemic treatment

Abstract

Objective.

To investigate the course of temporomandibular joint (TMJ) inflammation, osseous deformation and mandibular ramus growth in children with juvenile idiopathic arthritis (JIA) during systemic therapy.

Methods.

Longitudinal study of 38 consecutive JIA patients (29 female, median age 9.0 years, interquartile range 6.2 to 10.7 years) on systemic therapy with TMJ involvement, with two TMJ magnetic resonance imaging (MRI) examinations ≥ 2 years apart and no TMJ corticosteroid injection. Clinical and MRI findings were compared between initial and follow-up examinations and between TMJs with and without active inflammation at baseline.

Results.

Over a median period of 3.6 years (range, 2.0–8.7 years), MRI grade of TMJ inflammation improved (p=0.009) and overall osseous deformity tended to become less severe (p=0.114). In TMJs with arthritis at baseline (46 TMJs), both the grades of inflammation (p<0.001) and deformity (p=0.011) improved. In TMJs with no arthritis at baseline (30 TMJs), the frequency and grade of condylar deformation remained stable. Mandibular ramus growth rates were not significantly different between TMJs with and without arthritis at baseline (1.3 mm/year versus 1.5 mm/year, p=0.273), and were not correlated with the degree of inflammation at baseline or follow-up.The frequency of facial asymmetry tended to be lower at follow-up than at initial examination (24% versus 45%, p=0.056).

Conclusion.

Our results suggest that systemic treatment of TMJ arthritis in children with JIA decreases the degree of inflammation seen on MRI, preserves osseous TMJ morphology and maintains normal mandibular ramus growth.

Introduction

Involvement of the temporomandibular joint (TMJ) is common in patients with juvenile idiopathic arthritis (JIA), with an estimated frequency of about 40 - 60% based on large imaging series in the literature (1, 2). As inflammation of the TMJ is suspected to be the cause for craniofacial growth disturbances frequently seen in patients with JIA (3), early detection and prompt treatment of arthritis is currently thought to be essential for normal development of the TMJ and mandible in growing children.

Because TMJ arthritis may often be asymptomatic and difficult to diagnose clinically (4, 5), contrast-enhanced magnetic resonance imaging (MRI) is considered the best available method for early diagnosis (6). In addition, MRI allows for grading the level of inflammation in the TMJ as well as assessment of the osteochondral joint morphology and height of the mandibular ramus (7-9).

Our group has previously shown that intraarticular corticosteroid injections in a cohort of 33 children with JIA did neither preserve normal growth of the mandibular ramus over a median period of 5 years, nor were they able to prevent progressive TMJ deformity (10).

With this study, we aimed to evaluate mandibular growth, the course of inflammation and deformity of the TMJ in children who underwent systemic immunosuppressive treatment for JIA.

Material and Methods

Patients

For this retrospective study, we identified 38 consecutive children seen at our tertiary paediatric university hospital between 2006 and 2015 with a diagnosis of JIA according to the International League of Associations for Rheumatology 2001 criteria (11), MRI diagnosis of TMJ involvement (TMJ arthritis and/or TMJ deformity presumed to be the result of arthritis) and an MRI follow-up after 2 or more years. During this period, we saw 479 JIA patients in our outpatient clinics and MRI was performed routinely at a time point when TMJ involvement had a potential implication for treatment (12). Patients without systemic immunosuppressive treatment and those who received any corticosteroid injections in the TMJ were excluded from the study. Children with no consent for retrospective data analysis were not considered. The study was conducted according to Swiss legislation and approved by the governmental research ethics committee (KEK ZH 2015-0433).

Patient data, including results of clinical examinations and medication during the observation period, were retrieved from the electronic patient files. The study population consisted of 29 girls and 9 boys, with a median age of 9.0 years at first MRI (age range 1.5 – 13.7 years, IQR 6.2 – 10.7 years) and a median age of 6.8 years at initial diagnosis of JIA (age range 1.2 - 12.8 years, IQR 3.3 – 9.0 years). The follow-up MRI evaluated for this study was performed after a median interval of 3.6 years (range 2.0 – 8.7 years, IQR 2.6 – 4.7 years). The patient characteristics of the study population are summarised in table 1. The terminology used in this work adheres to the recommendations by the TMJ juvenile arthritis working group (13).

Clinical examination

Clinical assessment of the TMJ was performed as routine care at regular intervals by experienced paediatric rheumatologists and orthodontists (14). Results of the examination closest to the respective MRI were used for this study (median interval between clinical assessment and MRI 0 days, IQR -2.2 to 0.8 months). Presence of TMJ pain as reported by the patient and on palpation in a relaxed position of the mandible and during movement was noted. Mandibular skeletal asymmetry was graded as absent (0), mild (± 1) or severe (± 2) with a deviation to the right (positive value) or to the left (negative value). Maximal mouth opening capacity (MOC), i.e. the unassisted greatest inter-incisal distance without adjustment for overbite, was measured with an acrylic ruler after the patient opened the mouth as wide as possible several times for warm-up. Centiles of MOC were calculated from normal age- and gender- adjusted values (15).

MRI evaluation

All contrast-enhanced MRI of the TMJ was performed at 1.5 Tesla (Signa MR/i Twinspeed or Discovery MR450, GE Medical Systems, Milwaukee, USA) with a TMJ surface coil in closed mouth position according to the institutional protocol (10). The MRI studies were reviewed by an orthodontist (AB) and a paediatric radiologist (CJK) in a consensus reading. As described previously (8, 10), TMJ involvement was graded with a progressive scoring system (Appendix). Presence and degree of joint effusion, synovial thickening, and bone marrow oedema were assessed on fat-saturated T2-weighted images. Presence and extension of joint enhancement was assessed on early contrast-enhanced images. Inflammatory activity of the TMJ was graded semi quantitatively on a 5-grade scale (grades 0–4). Shape and integrity of the temporal bone (articular eminence and glenoid fossa) and mandibular condyle were assessed on gradient echo images. Osseous deformity was

also graded semi quantitatively on a 5-grade scale. Mandibular ramus height was measured on minimum intensity projection images from a three-dimensional (3D) gradient echo sequence, on a line parallel to the posterior border of the ramus through the most cranial point of the condyle to the intersection with the inferior border of the ramus (9) . From the mandibular height at the initial MRI and follow-up MRI, growth rates were calculated for each mandibular ramus, and compared to normal age- and gender-matched growth rates based on longitudinal cephalographic measurements between the condylion and gonion in 102 children from 3 to 16 years of age (16, 17).

Comparisons and statistical analysis

Descriptive data are given as mean ± standard deviation for continuous variables with normal distribution and as median (interquartile range) for variables without normal distribution. Normal distribution of the data was checked with the Shapiro-Wilk test. Frequencies are reported as fractions (percentage).

The clinical findings were compared between initial and follow-up examination with the chi squared test for frequencies, Wilcoxon test for ordinal and not normally distributed data, and paired sample t-test for data with normal distribution. TMJ pain, MOC and facial asymmetry were correlated to MRI findings with Spearman rank correlation.

The MRI findings were compared between initial and follow-up studies for TMJs with and without active inflammation at baseline, and between TMJs with and without active inflammation at baseline. Frequencies of MRI findings at initial and follow-up examinations were compared with the chi squared test. Mandibular ramus height, grades of inflammation and grades of deformity were compared with the Wilcoxon test between MRI examinations. Mandibular ramus growth rates were compared between TMJs with and without active inflammation at baseline with the Mann-Whitney test. Measured growth rates were compared to expected normal growth rates with the Wilcoxon test. Growth rates were correlated with the grades of inflammation and deformity at initial and follow-up MRI using Spearman rank correlation. All statistical analyses were performed with MedCalc Statistical Software version 18.11.3 (MedCalc Software bvba, Ostend, Belgium). A p-value < 0.05 was considered significant.

Results

Medication

The indication for systemic immunosuppressive therapy was arthritis of multiple joints (n=30, peripheral joints and TMJs), arthritis of the spine or sacroiliac joints (n=5), or uveitis (n=2). In only one patient severe TMJ arthritis was the main indication for systemic treatment, at a time when we no longer offered intraarticular corticosteroid injections to the TMJ. Before 2013, we would have considered corticosteroid injection in the case of isolated TMJ arthritis or when peripheral arthritis was under control by local therapy.

In 19/38(50%) children the systemic medication was started 2.3 (IQR 4.4 to 0.9) years before the first MRI study. In the other half of the children, systemic medication was introduced at or after first MRI with a median interval of 0.5 (IQR 0.1 to 1.6) years. The median duration of systemic therapy between the initial and follow-up MRI was 3.0 (IQR 1.9 to 4.2) years corresponding to 96% (IQR 72% to 100%) of the observation period.

Systemic medication included methotrexate (MTX) in 35/38(92%) patients. During the observation period, MTX was substituted by another drug in 19/38(50%) patients: leflunomide in 9 cases, etanercept in 6 cases, infliximab in 2 cases, and golimumab in 2 cases. MTX or leflunomide was combined with another drug in 20/38(53%) patients: golimumab in 9 cases, etanercept in 9 cases or tocilizumab in 2 cases. Two patients were treated with hydroxychloroquine and one patient with a combination of systemic corticosteroids, azathioprine and golimumab.

Clinical findings

The clinical findings at the initial and follow-up examinations are summarised in table 2. Tenderness was reported in different TMJs at baseline and at follow-up, with low frequencies of 13% and 9% respectively. Presence of TMJ pain did not correlate with MRI grades of inflammation or deformity. Mandibular skeletal asymmetry was noted in 17/38(45%) patients initially and in 9/38(23%) patients at follow-up, with resolution of mild asymmetry in 10 patients, but development of mild asymmetry and deterioration of mild to severe asymmetry in 2 patients each. Presence and degree of asymmetry were not significantly different between initial and follow-up examination, but the frequency of asymmetry tended to be lower at follow-up (17/38 initially, versus 9/38 at follow-up, p=0.056). The degree of asymmetry showed a weak correlation with the grade of TMJ deformity (r_s = 0.316, p = 0.005). The mean MOC improved by 4.4 mm (95% confidence interval 2.7 to 6.2 mm, p<0.0001), but age- and gender-adjusted centiles of MOC were not significantly different (mean

difference 1.6, 95% confidence interval -6.4 to 9.7, p=0.680) between initial and follow-up assessment. Both absolute values and centiles of MOC showed no correlation with MRI grades of inflammation or deformity.

MRI findings

The prevalence of TMJ arthritis (active inflammation) was 27/38(71%) patients at baseline and 23/38(61%) patients at follow-up. TMJ deformity was seen in 22/38(59%) patients initially and in 21/38(55%) patients at follow-up. Initially 7/38(18%) patients had unilateral and 15/38(39%) bilateral deformity. During the study period, 4/38(11%) patients developed unilateral and 1/38(3%) bilateral deformity, while in 4/38(11%) patients unilateral deformity and in 1/38(3%) bilateral deformity resolved. In another 1/38(3%) patients bilateral deformity improved to unilateral deformity. Therefore the overall frequency of unilateral and bilateral deformity was not significantly different at follow-up: 7/38(18%) patients had unilateral and 14/38(37%) bilateral TMJ deformity.

At initial MRI 46/76(61%) TMJs showed signs of inflammation (grade > 0) and 37/76(49%) TMJs had some deformity (grade > 0). At follow-up MRI 40/76(54%) TMJs showed signs of inflammation and 35/76(46%) TMJs were deformed. Overall, grades of inflammation improved (p=0.009) while grades of deformation were not significantly different (p=0.114) at follow-up. The inflammatory and deformity grades at the initial and follow-up MRI are detailed in table 3 for all TMJs and groups of TMJs with and without inflammation at baseline. No TMJ showed the most severe grade of inflammation (inflammatory activity grade 4, TMJ filled with and expanded by pannus), large erosions, fragmentation of the condyle or intraarticular calcification (deformity grade 4).

In the TMJs without inflammation at baseline, signs of inflammation were seen at follow-up in 10/30(33%) TMJs, while the frequency and grades of deformation were not significantly different between initial and follow-up MRI.

In the TMJs with inflammation at baseline, the frequency and grades of inflammation improved significantly (p<0.001) at follow-up, as did the grades of deformity (p=0.011).

Inflammatory grades at follow-up MRI were lower for TMJs without inflammation at baseline than for TMJs with inflammation at baseline (Mann-Whitney test, p=0.018). Deformation grades were not significantly different between TMJs with and without inflammation at baseline both at initial (Mann-Whitney test,

p=0.454) and follow-up MRI (Mann Whitney test, p=0.154). The change of inflammation and deformity grades between initial and follow-up MRI for both groups are given in table 4.

The height of the mandibular ramus increased by a median difference of 5.2 mm (95% confidence interval 4.5 mm to 5.9 mm, Wilcoxon test, p<0.0001) from initial to follow-up MRI with a median growth rate of 1.4 mm/year (95% confidence interval 1.2 mm to 1.6 mm). At both MRI studies, the mandibular ramus height was not significantly different between TMJs with and without inflammation or deformation at baseline (Table 5). The growth rates were not significantly different between TMJs with and without inflammation at baseline but tended to be lower in the TMJs with inflammation (median difference -0.2 mm/year, Mann-Whitney test, p=0.273). Overall, the observed growth rates were not significantly different from normal (Figure 1 and Table 5) (16, 17). TMJs with inflammation at baseline tended to have lower growth rates than normal (median difference - 0.15 mm/year, Wilcoxon test, p=0.140) while TMJs without inflammation at baseline showed no difference (median difference 0.04 mm/year, Wilcoxon test, p=0.665). The growth rate did not correlate with the grade of inflammation at initial or follow-up MRI, but showed a weak negative correlation with the degree of deformity at initial (r_s=-0.257, p=0.025) and at follow-up MRI (r_s=-0.399, p<0.001).

Discussion

With this longitudinal study we describe the course of TMJ deformity, TMJ inflammation and clinical findings in 38 children with JIA on systemic therapy over a median period of 3.6 years (range 2 – 8.7 years). Recent reviews have indicated that there is not much data evaluating the efficacy of contemporary systemic treatment on TMJ involvement in patients with JIA (18, 19). While there is anecdotal evidence that systemic therapy may decrease progressive radiographically evident destructive changes of the TMJ and clinically seen facial deformities (19), only two series observed that systemic therapy may be effective in this regard (20, 21). The study by Ince et al suggested that MTX therapy may minimize TMJ destruction in polyarticular JIA, because 18 patients receiving MTX showed less severe TMJ involvement than 9 patients not receiving MTX. In a longitudinal study of 84 children with JIA, Twilt et al showed that the prevalence of patients with condylar alterations decreased from 49% to 40% over 5 years when assessed on orthopantomographs, but this improvement was associated with low disease activity and a less extensive therapeutic regimen (21). Before the widespread use of MTX therapy, Arvidsson et al observed progression of radiographic condylar and temporal bone abnormalities from 42% of 60 children with JIA at baseline to 65% at a 4-year follow-up

examination in the early 1980s (22). In our study, we found a slightly higher prevalence of condylar deformity at baseline (22/38 patients, 59%) which was not significantly different at follow-up (20/38 patients, 53%). The overall frequency and degree of TMJ deformation did not change significantly between the MRI studies, but TMJs with arthritis at baseline showed an improvement of the condylar deformity at follow-up (p=0.011). In addition, we did not observe any progressive TMJ destruction or intraarticular calcification (deformity grade 4), which in contrast had developed rather frequently (26% progressive TMJ destruction, 20% intraarticular calcification) in our previous series of 33 children treated with intraarticular corticosteroid injection (10). The absence of severe progressive condylar destruction in the current patients on systemic therapy may explain why the mandibular ramus growth rate remained normal, while it was significantly lower than normal in the aforementioned patients treated with TMJ corticosteroid injection.

The maintained normal mandibular ramus growth and improvement of condylar deformity in TMJs with arthritis at baseline may be the basis for our observation that mandibular skeletal asymmetry tended to decrease in the patients of the current study. This may suggest that systemic treatment could be contributory in preventing craniofacial deformity attributed to impaired mandibular ramus growth resulting from TMJ arthritis in children with JIA. Alternatively, the trend to lower facial asymmetry could just be manifestation of normal variation during growth (23).. The current pathophysiological assumption is that disease modifying antirheumatic drugs reduce inflammation in the TMJ and therefore allow for normal development of the condyle and growth of the mandibular ramus at the condylar growth zone. This hypothesis is supported by our cohort in three ways. Firstly, we found significantly less inflammation in TMJs at follow-up than at baseline. Secondly, mandibular ramus growth rate was negatively correlated with condylar deformity. Thirdly, the mandibular ramus growth rate was normal, albeit it tended to be lower in TMJs with than without inflammation at baseline. To our surprise, there was no correlation between the degree of inflammation seen on MRI and the growth of the mandibular ramus. This may indicate that TMJ arthritis was sufficiently controlled in our patients. However, this finding may also indicate that growth is not so much influenced by the inflammation per se, but growth impairment is the result of the structural damage to the growth zone of the mandibular condyle, which again is supported by the observed negative correlation of the growth rate with condylar deformity. The fact that mandibular ramus growth may be normal despite the presence of low grade inflammation on MRI could be used as an argument against treating TMJ arthritis aggressively with intraarticular corticosteroids. Another argument against intraarticular corticosteroids would be that we want to

avoid the risk of creating steroid-induced severe TMJ deformities because that has a negative impact on mandibular growth.

The clinical findings in this cohort confirm that orofacial examination has a poor diagnostic value for predicting the presence of TMJ arthritis (14, 24). Pain was present in only 13% and 9% of TMJs at initial and follow-up examination and did not correlate with MRI signs of inflammation or deformity. Overall, MOC was normal at initial and follow-up examination, and did not correlate with the MRI findings. Facial asymmetry was not significantly different between examinations but tended to improve at follow-up (p=0.056).

The main limitation of our study is its retrospective and uncontrolled design with variable medication and imaging intervals. From our results, it is not possible to draw any conclusions on the efficacy of different medications or combinations thereof. By just examining the patients at two time points, we cannot account for possible effects of TMJ arthritis fluctuation on the observed changes. The study cohort reflects our current praxis to treat JIA with systemic medication in cases with severe TMJ inflammation or when local treatment of other joints is not sufficient to control disease activity. MRI of the TMJ was usually conducted when the presence of TMJ inflammation would have changed the treatment approach or for assessing treatment response of confirmed TMJ arthritis. By only measuring the height of the mandibular ramus, we did not account for all components of vertical mandibular growth. Evaluation of appositional growth, changes in the gonion area, antegonial notching and backward-rotation of the mandibular corpus would require cephalography or three-dimensional computed tomography, which was not available in our patients. Nonetheless, by showing normal growth of the mandibular ramus height we assume normal condylar growth that is not impaired by TMJ arthritis. The use of historical cephalographic data for normal mandibular ramus growth is another limitation to our growth assessment. To our knowledge this is the only available data in the literature that allows calculation of normal mandibular ramus growth rate. The fact that the growth rates in both our groups of TMJs with and without arthritis at baseline did not differ from the historical normal growth rates suggests that they may still be accurate.

Another limitation is the measurement error of our assessment methods, which may not allow measuring short-term mandibular ramus growth and change of MRI findings in the TMJ accurately in a single patient. According to Markic et al (9), MRI measurements of the mandibular ramus height can be performed with a mean difference of 0.2 mm (95% limits of agreement -2.4 – 2.9 mm). With a mean normal growth rate of 1.6 mm/year (range 0.7 – 2.8 mm/year) (16, 17), short-term growth rates over 3 months may show a mean

measurement error of up to ± 50%, whereas for long-term growth rates over 5 years the mean measurement error is estimated at ± 5%. The grading of the TMJ inflammation and deformity was performed by two readers in consensus, in order to improve reliability of our assessment. The reliability of the applied grading system has been tested elsewhere (25) showing high reliability both for the inflammatory and deformity domain (average-measure ICC 0.92 and 0.96) and excellent smallest detectable differences (29% and 23%). While these measurement errors may be substantial when assessing a single TMJ, they should be cancelled out when comparing mean growth rates and MRI scores of groups of joints as done in the current work.

Further studies are needed to support the portrayed findings, and should especially focus on evaluating the efficacy of different systemic medications and address the long term effect on TMJ morphology and overall craniofacial development.

In conclusion, with this retrospective longitudinal study we suggest that systemic treatment of TMJ arthritis in children with JIA may reduce inflammatory changes seen on MRI, preserves osseous TMJ morphology and maintains normal mandibular ramus growth over a period of at least 2 years. This is clearly in contrast to an earlier cohort treated with corticosteroid TMJ injections, in which TMJ deformity deteriorated and mandibular ramus growth was impaired. Our findings are also in stark contrast to the body of literature from the pre-therapeutic era of JIA, at least with respect to growth and damage.

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Figure legends

Figure 1. Notched box and whisker plot showing the mandibular ramus growth rate in 38 patients (76 TMJs) during a median follow-up of 3.6 years (range 2 – 8.7 years, interquartile range 2.6 – 4.7 years) in comparison to the mean age- and gender-matched normal growth rate (p=0.360, Wilcoxon test). Normal growth rates were calculated from annual increments of cephalographic measurements between condylion and gonion in 102 children from 3 to 16 years of age (16, 17). The central box represents the values from the lower to upper quartile (25^{th} to 75^{th} percentile), the middle line represents the median and the whiskers represent the minimum and maximum values with exclusion of outside values (a value that is smaller than the lower quartile minus 1.5 times the interquartile range or larger than the upper quartile plus 1.5 times the interquartile range).

Table 1. Patient characteristics of 38 children with JIA on systemic therapy and TMJ involvement.

Patient characteristics	
Female, n (%)	29 (76)
Oligoarticular, n (%)	7 (18)
Oligoarticular extended, n (%)	5 (13)
Polyarticular RF negative, n (%)	17 (45)
Enthesitis-related arthritis, n (%)	2 (5)
Psoriasis arthritis, n (%)	2 (5)
Systemic arthritis, n (%)	1 (3)
Not classified arthritis, n (%)	4 (11)
Age at diagnosis, median (IQR), years	6.8 (3.3 – 9.0)
Age at initiation of systemic medication, median (IQR), years	8.1 (4.8 – 9.9)
Age at first MRI, median (IQR), years	9.0 (6.2 – 10.7)
Disease duration at first MRI, median (IQR), years	1.2 (0.3 – 2.7)
MRI follow-up, median (IQR), years	3.6 (2.6 – 4.7)
Duration of systemic medication between MRI studies, median (IQR), years	3.0 (1.9 – 4.2)

RF rheumatoid factor, *IQR* interquartile range, *MRI* magnetic resonance imaging.

Table 2. Clinical findings in 38 patients with JIA on systemic therapy and TMJ involvement.

			Initial examination	Follow-up examination	P-value
Tenderness (76 TMJs)			10/76 (13%)	7/76 (9%)	0.432 *
Asymmetry:	Frequency		17/38 (45%)	9/38 (24%)	0.056 *
	Grade	None, 0	21/38 (55%)	29 /38 (76%)	0.173 **
		Mild, -1, 1	16/38 (42%)	6/38 (16%)	
		Severe, -2, 2	1/38 (3%)	3/38 (8%)	
MOC,	mm (mean ± SD)		44 ± 8 mm	49 ± 8 mm	< 0.001 ***
	centiles (mean ± SD):		51 ± 33	53 ± 29	0.680 ***

TMJ temporomandibular joint, *MOC* mouth opening capacity, *SD* standard deviation, comparison between initial and follow-up examination with * chi squared test, ** Wilcoxon test, *** paired samples t-test.

Table 3. MRI findings in 38 patients with JIA on systemic therapy and TMJ involvement.

			Initial MRI	Follow-up MRI	P-value
All TMJs (n=76)	Inflammation: Frequency		46/76 (60.5%)	40/76 (53.6%)	0.392 *
	Grade	0	30/76 (39.5%)	36/76 (47.4%)	0.009 **
		1	28/76 (36.8%)	36/76 (47.4%)	
		2	14/76 (18.4%)	4/76 (5.3%)	
		3	4/76 (5.3%)		
	Deformation: Frequency		37/76 (48.7%)	35/76 (46.1%)	0.749 *
	Grade	0	39/76 (51.3%)	41/76 (53.9%)	0.114 **
		1	23/76 (30.3%)	27/76 (35.5%)	
		2	9/76 (11.8%)	5/76 (6.6%)	
		3	5/76 (6.6%)	3/76 (3.9%)	
TMJs without inflammation at baseline (n=30)	Inflammation: Frequency		0/30 (0%)	10/30 (33.3%)	<0.001 *
	Grade	0	30/30 (100%)	20/30 (66.7%)	0.002 **
		1		8/30 (26.7%)	
		2		2/30 (6.7%)	
	Deformation: Frequency		13/30 (43.3%)	17/30 (56.7%)	0.303 *
	Grade	0	17/30 (56.7%)	13/30 (43.3%)	0.375 **
		1	8/30 (26.7%)	13/30 (43.3%)	
		2	4/30 (13.3%)	3/30 (10.0%)	
		3	1/30 (3.3%)	1/30 (3.3%)	
TMJs with inflammation at baseline (n=46)	Inflammation: Frequency		46/46 (100%)	30/46 (65.2%)	<0.001 *
	Grade	0	0/46 (0%)	16/46 (34.8%)	<0.001 **
		1	28/46 (60.9%)	28/46 (60.9%)	
		2	14/46 (30.4%)	2/46 (4.3%)	
		3	4/46 (8.7%)		
	Deformation: Frequency		24/46 (52.2%)	18/46 (39.1%)	0.210 *
	Grade	0	22/46 (47.8%)	28/46 (60.9%)	0.011 **
		1	15/46 (32.6%)	15/46 (30.4%)	
		2	5/46 (10.9%)	2/46 (4.3%)	
		3	4/46 (8.7%)	2/46 (4.3%)	

TMJ temporomandibular joint, comparison between MRI studies with * chi squared test, ** Wilcoxon test.

Table 4. Change of inflammation and deformity grades from initial to follow-up MRI in 76 TMJs of 38 patients with JIA on systemic therapy and TMJ involvement

		TMJs without inflammation at baseline	TMJs with inflammation at baseline
Grade of inflammation	Improved	na	26/46(57%)
	Stable	20/30(67%)	19/46(41%)
	Deteriorated	10/30(33%)	1/46(2%)
Grade of deformity	Improved	2/30(7%)	12/46(26%)
	Stable	23/30(77%)	31/46(67%)
	Deteriorated	5/30(17%)	3/46(7%)

TMJ temporomandibular joint, *na* not applicable

Table 5. Mandibular ramus height and growth rates in 38 patients with JIA on systemic therapy and TMJ involvement

	Mandibular ramus height (mm)		Growth rate (mm/year)	Normal growth rate (mm/year)	P-value *
	At initial MRI	At follow-up MRI			
All TMJs (n=76)	48.5(43.3-51.8	53.9(48.1-57.9)	1.4(1.0-1.9)	1.4(1.4-1.6)	0.360
TMJs without inflammation at baseline (n=30)	48.0(44.1-50.7)	53.8(49.7-60.0)	1.5(1.2-2.0)	1.4(1.4-1.6)	0.665
TMJs with inflammation at baseline n=46)	49.1(42.4-52.3)	53.9(47.7-57.4)	1.3(1.0-1.8)	1.4(1.4-1.6)	0.140
TMJs without deformity at baseline (n=39)	47.8(42.4-51.7)	53.2(47.8-59.5)	1.5(1.0-2.0)	1.4(1.4-1.6)	0.734
TMJs with deformity at baseline (n=37)	48.8(44.5-51.9)	54(50.9-57.2)	1.3(1.1-1.7)	1.4(1.3-1.5)	0.294

Data are given as median (interquartile range), * comparison between measured growth rates and age- and gender matched normal growth rates with Wilcoxon test.

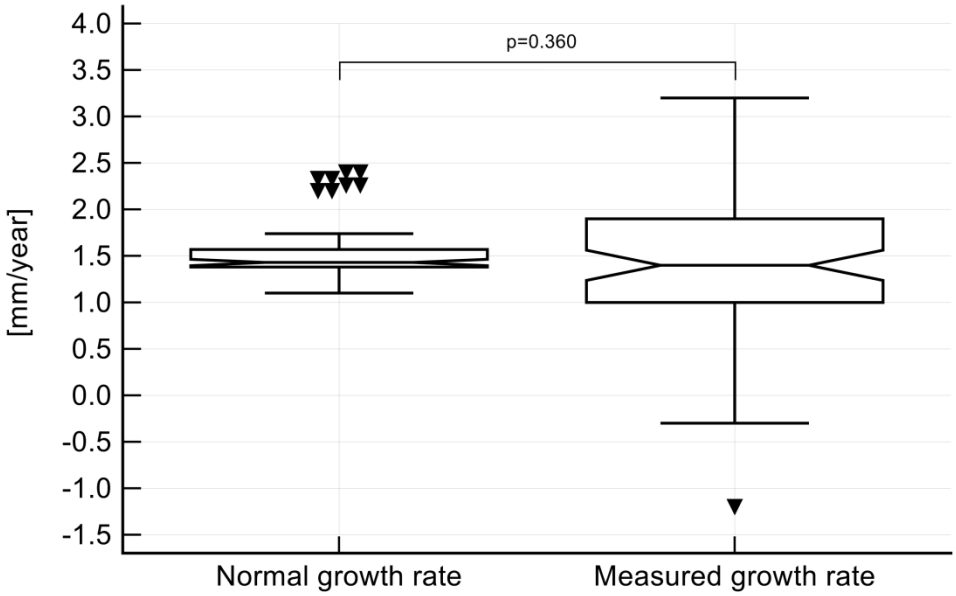

Figure 1. Notched box and whisker plot showing the mandibular ramus growth rate in 38 patients (76 TMJs) during a median follow-up of 3.6 years (range 2 – 8.7 years, interquartile range 2.6 – 4.7 years) in comparison to the mean age- and gender-matched normal growth rate (p=0.360, Wilcoxon test). Normal growth rates were calculated from annual increments of cephalographic measurements between condylion and gonion in 102 children from 3 to 16 years of age (16, 17). The central box represents the values from the lower to upper quartile (25th to 75th percentile), the middle line represents the median and the whiskers represent the minimum and maximum values with exclusion of outside values (a value that is smaller than the lower quartile minus 1.5 times the interquartile range or larger than the upper quartile plus 1.5 times the interquartile range).

155x99mm (600 x 600 DPI)

Appendix. Progressive MRI score for assessing inflammatory activity and osseous deformity of the TMJ

Grade	Inflammatory activity	Osseous deformity
0	No inflammation: No or small amount of joint fluid. No enhancement or enhancement confined to physiological amount of joint fluid.	Normal shape of temporal bone and mandibular condyle: S-shaped articular eminence/glenoid fossa. Round condyle (young patient). Less rounded, more angular appearing condyle (older patient). Intact and smooth subchondral bone contour.
1	Mild inflammation: Extension of joint enhancement exceeds that of physiological joint fluid but does not involve entire joint compartment and/or presence of bone marrow oedema.	Mild flattening of mandibular condyle and/or temporal bone.
2	Moderate inflammation: Joint enhancement involves entire joint compartment or there is an enhancing joint effusion.	Moderate flattening of mandibular condyle and/or temporal bone.
3	Severe inflammation: Detectable synovial thickening in addition to increased joint enhancement or effusion.	Severe flattening of mandibular condyle with loss of height and/or completely flat temporal bone. ± small erosions/irregularities of subchondral bone
4	Joint space filled with and expanded by pannus	"Destruction" of temporomandibular joint by large erosions, fragmentation of mandibular condyle, intraarticular ossification or bone apposition on condyle or temporal bone.